

# **ORIGINAL ARTICLE**

# Reducing intravenous antibiotics in neonates born ≥35 weeks' gestation: A quality improvement study

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**Aim:** To assess the impact of the Early Onset Sepsis (EOS) calculator, implemented as a quality improvement study, to reduce the rate of unnecessary antibiotics in neonates born ≥35 weeks' gestation.

**Methods:** An audit of routinely collected hospital data from January 2008 to March 2014 (retrospective) and from January 2018 to September 2019 (prospective) determined baseline incidence of EOS intravenous antibiotic use in neonates born  $\geq$ 35 weeks' gestation in a tertiary level perinatal centre. Plan-do-study-act (PDSA) cycles were applied to implement the EOS calculator. Statistical process control methodology and time series analysis assessments were used to assess the potential impact of the PDSA cycles on the rate of intravenous antibiotics, blood culture collection, EOS, length of stay and health care costs (not adjusted for potential confounders).

**Results:** In the study population, from January 2008 to March 2014, the baseline incidence of intravenous antibiotic use was 10.49% (2970/28290), whilst only 0.067% (19/28290) neonates had culture proven EOS. From January 2018 to October 2019, prior to implementation of the EOS calculator, 13.3% (1119/8411) neonates were treated with intravenous antibiotic and the use decreased to 8.3% (61/734) post-implementation. The rate of blood culture collection decreased from 14.4% (1211/8411) to 11.9% (87/734). There were no cases of missed EOS. Length of stay decreased from 2.68 to 2.39 days, with an estimated cost saving of \$366 per patient per admission.

**Conclusion:** Implementing the EOS calculator in a tertiary hospital setting reduced invasive investigations for EOS and intravenous antibiotic use among neonates  $\geq$ 35 weeks' gestation. This can result in reduced length of neonatal hospital stays, and associated health care cost savings and may reduce separation of mother and baby.

Key words: antimicrobial stewardship; early onset neonatal sepsis; quality improvement.

#### What is already known on this topic

- 1 A substantial number of near term and term neonates receive early life antibiotics unnecessarily due to perceived risk of sepsis exceeding the actual rate of sepsis.
- 2 Unnecessary antibiotic use is not without risk and is associated with short- and long-term adverse effects for the baby, separation of mother and baby, a longer length of stay and increased health care costs.
- 3 More accurate methods of assessing which neonates need empiric antibiotics for risk of sepsis, with efforts made to avoid antibiotics in neonates without sepsis, are required.

#### What this paper adds

- 1 The use of intravenous antibiotics in neonates born  $\ge$ 35 weeks' gestation was almost 150-fold higher than the incidence of EOS at our hospital over a seven-year period.
- 2 The Quality Improvement approach overcame contextual barriers to allow successful implementation of the EOS calculator resulting in substantial and safe reduction in intravenous antibiotic use.
- 3 Whilst the calculator was validated in US population, this study builds on evidence that the EOS calculator can be implemented in the Australasian setting.

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Neonatal early onset sepsis (EOS), an invasive bacterial infection occurring in early life, is associated with significant morbidity and mortality.<sup>1,2</sup> Whilst exact timing of onset from birth can vary, in Australia neonatal EOS is typically defined as infection occurring in the first 48 h of life.<sup>2,3</sup> The diagnostic gold standard is growth of pathogenic bacteria in blood and/or cerebrospinal fluid.<sup>2,4</sup> Group B streptococcus (GBS), *Escherichia coli*, and other maternal

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genitourinary tract organisms are most commonly responsible.<sup>5</sup> Diagnosing neonatal sepsis is difficult as early clinical signs are subtle and non-specific, and laboratory results are often not diagnostic,<sup>5</sup> thus treatment is typically based on risk factors. Routine screening and intrapartum antibiotics for GBS colonisation has resulted in reduced rates of neonatal sepsis. An Australasian study found that the neonatal GBS sepsis rate was 1.43/1000 live births in 1993 falling to 0.25/1000 in 2001 with routine intrapartum prophylaxis.<sup>6</sup> Treatment for EOS in excess to actual EOS remain problematic.<sup>7</sup>

Long-term adverse effects of early life antibiotics, including atopy and obesity, are increasingly recognised.<sup>8,9</sup> Furthermore, high rates of antibiotic use contribute to the emergence of multiresistant organisms. Neonatal antimicrobial prescribing practices contribute to this global public health issue.<sup>10</sup>

Prior to this quality improvement (QI) project, a neonate at the Women's and Children's Hospital, Adelaide would be deemed at risk of EOS in the setting of maternal chorioamnionitis or inadequate maternal intrapartum antibiotics with prolonged rupture of membranes (PROM) or GBS colonisation; or spontaneous preterm labour. These neonates would typically be admitted to the nursery for monitoring, intravenous (IV) cannula insertion, collection of blood culture (BC), full blood examination (FBE) and blood gas and receive empiric IV antibiotics (IVABs) for a minimum of 48 hours.

Clinical staff had concerns that many well appearing neonates were treated for possible EOS, yet culture-positive sepsis was rare. This phenomenon of 'overtreatment' is well reported. For example, using CDC (Centers for Disease Control) based guide-lines, 15% of late preterm and term neonates are evaluated for EOS, and 8% are treated for EOS with IVABs,<sup>11</sup> yet the rate of culture positive EOS is <1/1000 live born infants.<sup>6,7,11</sup>

When reviewing the literature on strategies to reduce antibiotic exposure, the serial clinical examination approach and the Kaiser Permanente EOS calculator (EOSc) were identified as potential interventions.<sup>2,12</sup> The EOSc is an online tool that provides a risk assessment score based on maternal risk factors and neonatal clinical examination findings as well as guidance regarding treatment approach. It has been validated for clinical use.<sup>13</sup> After discussion among the QI team and clinical staff, the EOSc was selected as the potential health care intervention. The perceived 'safety' of taking BCs, in addition to the serial observations that form part of the EOSc recommendations for at-risk neonates, increased acceptability and clinician comfort with the intervention. The numerical risk score provided by the EOSc was also desirable. Consequently, we examined the impact of implementing the EOSc in our site to reduce unnecessary antibiotic exposure.

#### Aim

To safely reduce the rate of IVABs by 40% in neonates born  $\geq$ 35 weeks' gestation by implementing an EOSc.

## Methods

We utilised a standard QI plan-do-study-act (PDSA) model. Fundamental elements of the Evidence-based Practice for Improving Quality (EPIQ) programme<sup>14</sup> guided the study process. Working within the context of organisational culture, drivers of change and potential barriers were identified. Evidence was combined with contextual knowledge to implement change. By working closely with frontline staff, we sought to overcome barriers to achieve a significant, sustainable, and safe practice change in approach to antibiotic use.

We chose our aim using a commonly utilised approach in QI, the SMART framework: Specific, Measurable, Achievable, Realistic and Timely. Kuzniewicz<sup>2</sup> demonstrated that implementation of the EOSc resulted in a reduction of early antibiotic prescription by 50%. In QI projects, the goal should be ambitious but attainable to ensure ongoing momentum. We chose a 40% reduction in antibiotics to ensure it was achievable.

The study was undertaken at the Women's and Children's Hospital, Adelaide, a tertiary centre with a delivery suite, a level 6 nursery with 17 neonatal intensive care beds, a 35 special care bed nursery, and a postnatal ward that cares for mothers and their neonates. The multidisciplinary QI team was made up by staff working across these areas. On average, there are around 4500 neonates born ≥35 weeks' gestation annually at the Women's and Children's Hospital, Adelaide.

Anecdotally, local rates of treatment for EOS were in excess to true rates of EOS. A retrospective audit was conducted to ascertain local incidence of EOS and IVABs use in neonates born ≥35 weeks gestation, to determine if proceeding with the study was worthwhile. Using clinical information services and pathology databases, we retrieved data regarding number of neonates born ≥35 weeks gestation from 2008 to 2014 who were investigated for risk of EOS (in the form of blood culture draw) and the number over the same period treated for risk of EOS with IVABs. Pathology data was reviewed; positive blood and CSF culture data was reviewed to determine the rate of EOS. An episode of EOS was defined as blood or CSF culture yielding pathogenic bacteria in the first 72 h of life. A bacteria was deemed pathogenic if it was not normal skin flora and not on the CDC list of known blood culture contaminants.<sup>15</sup> Assessment of EOS data from our hospital from 2008 to 2014 revealed that 10.4% neonates born ≥35 weeks gestation were treated with empiric EOS antibiotics, however only 0.067% had culture proven EOS. The pathology database with longest continuous data record was chosen to determine local incidence. This database stopped being in use in 2014 therefore the period from 2008 to 2014 provide information for the baseline EOS incidence and EOS treatment rate, gathered by a retrospective audit. After confirming that the rates of treatment for EOS far excessed rate of true EOS, the decision was to proceed with the study (see Supporting Information).

To collect contemporary data for real-time data analysis assessing the impact of interventions, a second audit assessing antibiotic use in the period leading up to the EOS calculator implementation, from January 2018 through to September 2019 was conducted. The rate of IVAbs use in this cohort of neonates had increased to 13.3%.

The QI team mapped the neonatal EOS risk assessment and management decision making process (see Supporting Information). A cause-and-effect diagram was developed, examining factors contributing to the high rates of empiric antibiotic prescriptions (see Supporting Information). A multi-voting process was used to determine the major contributing factors (see Supporting Information).

The QI team identified that for safe implementation of the EOSc, it was necessary to optimise the volume of blood collected for BC, standardise the documentation of EOS risk score and develop

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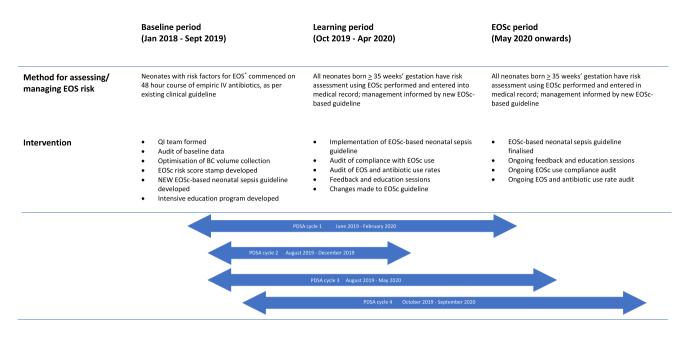


Fig. 1 Timeline of intervention and plan-do-study-act (PDSA) cycles. \*Risk factors for EOS risk: exposure to maternal chorioamnionitis; delivery after spontaneous onset of labour <37 weeks' gestation; inadequate maternal intrapartum antibiotics in the setting of GBS colonisation or rupture of membrane >18 h.

clinical guidelines for EOSc use. These elements formed the basis of the PDSA cycles. For each cycle, the intervention was studied and outcome measures were reviewed (Fig. 1), with results informing ongoing practice change (see Supporting Information).

#### PDSA cycle 1: Blood culture volume collection

This intervention coincided with another QI project in the nursery focusing on optimisation of the volume collected for BC, aiming for a minimum collection volume of 1 mL of blood, through education and feedback sessions.<sup>16</sup> The volume collected for BC was measured in the collection syringe with volumes recorded in patient notes and study record book. These were reviewed to check compliance with minimum volume collection (see Supporting Information).

#### PDSA cycle 2: EOS risk score stamp

Documentation of the EOSc risk score in patient medical records was standardised by developing an EOS risk score stamp. Compliance was monitored by intermittent medical record audits and results informed ongoing education strategies (see Supporting Information).

#### PDSA cycle 3: Development of clinical guideline

A clinical guideline was developed, accompanied by a caregiver information pamphlet about sepsis in neonates. This guideline was used in several 'Practice Run' PDSA cycles using theoretical patient data to allow assessment of useability of the guideline. Suggested changes to improve ease of use, including creation of single page flowchart, were implemented prior to guideline finalisation.

#### **PDSA cycle 4: EOS calculator**

Prior to implementation, intensive education regarding the EOSc occurred. The EOSc was implemented for use at the start of the Learning period (October 2019), along with the new EOSc based sepsis guideline. Ongoing staff education, feedback regarding usability of the EOSc and its guideline as well as impact on patient flow was sought. Suggested changes were implemented into practice and final implementation occurred EOS calculator period (May 2020) (Fig. 1).

The Baseline period (January 2018–September 2019) is defined as the period prior to use of the EOSc. During this period the EOSc education program and clinical guidelines were developed. From January 2018, the following outcomes were prospectively assessed monthly: (i) rate of IVABs given for risk of EOS in neonates born  $\geq$ 35 weeks' gestation defined as any IVABs received during admission (primary outcome); (ii) rate of investigation for EOS, assessed as BC collection taken in the first 4 days of life; (iii) rate of EOS (positive blood or CSF cultures). The Learning period (October 2019–April 2020) is defined as the period from when the EOSc was routinely used to assess EOS risk for all neonates born > 35 weeks' gestation, with a focus on education and familiarisation with the EOSc, and minor adjustment to guidelines. The EOSc implementation was complete in the EOSc period (May 2020 onward).

Rates for Baseline, Learning and EOSc periods were compared. After study completion, the length of stay (LOS) data, number of FBEs and blood gas investigations were reviewed. The Baseline period and study (Learning and EOSc) period data collection were complete.

To screen for missed EOS episodes, the neonatal population was identified by reviewing data in patients ≤28 days of age. The BC results between October 2019 and June 2020 were manually

screened and the medical records of neonates with positive cultures were reviewed. Additionally, Emergency Department presentations in patients ≤28 days of age were reviewed.

For birth admission LOS, we hypothesised the greatest impact of the EOSc on LOS would be in mothers and neonates that would otherwise have routine short stays. Consequently, the LOS data were based on the DRG P68D coding data corresponding to neonates born  $\geq$ 37 weeks' gestation with a birth weight of >2500 g. Using the National Hospital Cost Data Collection (NHCDC) Round 23, produced by the Independent Hospital Pricing Authority, we identified the fixed and variable cost components that made up the total cost attributable to this DRG (see Supporting Information).

We used standard QI study statistical process control methodology<sup>17</sup> (QI Macros package for Microsoft Excel 2020 (KnowWare International Inc., Denver, CO)). Data measurements in the study periods were plotted with upper and lower control limits and mean (centre line) on appropriate controls to determine if they constituted variation from the original process.<sup>18</sup> Special cause was defined as a single point outside the control limits; 8 or more consecutive points above or below the centre line; 6 consecutive points increasing or decreasing; 2 out of 3 consecutive points near a control limit (outer 1/3); and, or 15 consecutive points around the centre line (inner 1/3).<sup>19</sup> This study is reported in accordance with the SQUIRE 2.0 guidelines.

## Results

20%

18%

16%

12%

10%

oirth 14% uring

receiving ant

Percentage

UCL

In the Baseline period the rate of empiric IVABs use in neonates born ≥35 weeks' gestation at the Women's and Children's Hospital, Adelaide was 13.3% (1119/8411), with an EOS incidence of 0.7/1000 (19/28290 neonates) (see Supporting Information).

The overall rate of IVABs use decreased from an average of 13.3% (1119/8411) to 8.8% (276/3136) in the Learning period and the EOSc period. Special cause variation is seen (Fig. 2). Further analysis looking at the IVABs rate in the EOSc period only, the rate decreased further to 8.3% (61/734), a 37% reduction in the rate of IVABs

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The overall rate of BC collection in the first 4 days of life decreased from an average of 14.4% (1211/8411) to 11.2% (353/3136) in the Learning period and the EOSc period, with rate of 11.9% (87/734) in the EOSc period only. Special cause variation is seen (Fig. 3).

Since the implementation of the EOSc, two neonates born ≥35 weeks' gestation had culture proven EOS, one with GBS and the other E. coli. Both were appropriately commenced empirically on IVABs as per the EOSc recommendation. There were no identified cases of missed EOS.

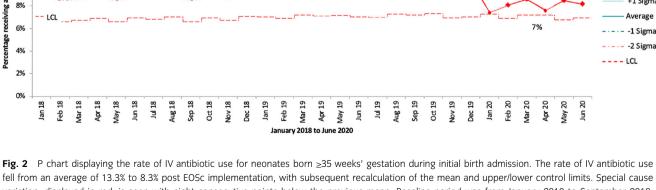
The LOS in otherwise uncomplicated neonates decreased from an average of 2.68 to 2.39 days during the EOSc period, equating up to an 11% reduction (Fig. 4).

Before implementation, the LOS was 2.68 days per patient, equating to a total cost per patient of \$4641.83. This was primarily comprised of variable costs (\$3384.89), which vary according to the length of stay. Post-implementation, LOS was 2.39 days per patient, with a total cost per patient of \$4275.55. The LOS cost savings per patient was \$366.28 (see Supporting Information).

Compliance with EOSc use increased over time. Audit of the EOS risk score stamp showed attempted completion rose from 85% in the Learning period to 88% in the EOSc period and correct completion rose from 55% to 74% (see Supporting Information).

Implementation of FOS calculator

17%



# Rate of IV antibiotic use in neonates born ≥ 35 weeks gestation

IVAB

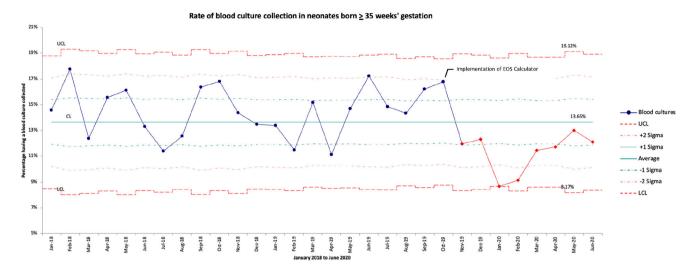
UCI

+2 Sigma

+1 Sigma

# variation, displayed in red, is seen with eight consecutive points below the previous mean. Baseline period was from January 2018 to September 2019; learning period from October 2019 to April 2020; EOS calculator period May 2020 to ongoing. The study period includes baseline period and up until June 2020. CL, centre line (mean); IVAB, intravenous antibiotics; LCL, lower control limit; UCL, upper control limit.

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**Fig. 3** P chart displaying the proportion of neonates born at 35 weeks or above having blood culture taken in the first 4 days of life. Overall rate of blood culture collection in the first 4 days of life fell from an average of 14.4% at baseline to 11.9% in the EOS calculator period, with subsequent recalculation of the mean and upper/lower control limits. Special cause variation, displayed in red, is seen with 8 consecutive points below the previous mean. Baseline period was from January 2018 to September 2019; learning period from October 2019 to April 2020; EOS calculator period May 2020 to ongoing. The study period includes baseline period and up until June 2020. CL, centre line (mean); LCL, lower control limit; UCL, upper control limit.

The average BC volume increased to 1.1 mL after PDSA cycle 1 (n = 450), whereas the baseline volume average was 0.6 mL. Compliance with a recommended minimum of 1 mL blood volume for inoculating BC bottles increased to 94% after PDSA cycle 1.

The monthly number of FBE in neonates collected in special care nursery, delivery suite and postnatal ward fell from an average of 673 per month to 594 after the Learning period (Fig. 5). After the Learning period, the blood gas collection rate fell from an average of 1544 to 1335 per month (Fig. 6).

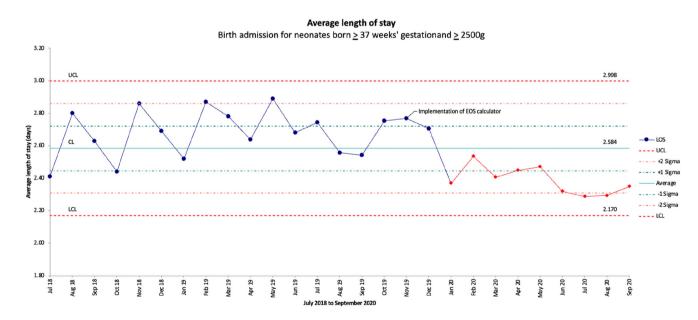
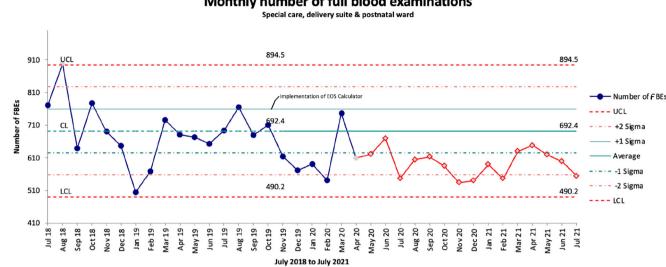


Fig. 4 X chart displaying the average length of hospital stay for neonates born greater than 37 weeks and ≥2500 g. Length of stay fell from an average of 2.68 to 2.39 days in the EOS calculator period. Special cause variation, displayed in red, is seen with eight consecutive points below the previous mean. Baseline period was from July 2018 to September 2019; learning period from October 2019 to April 2020; EOS calculator period May 2020 to ongoing. The study period includes baseline period and up until September 2020. CL, centre line (mean); LCL, lower control limit; LOS, length of stay; UCL, upper control limit.

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# Monthly number of full blood examinations

Fig. 5 X chart displaying the monthly number of full blood examinations for babies in the special care nursery, delivery suite and postnatal ward. Full blood examinations fell from an average of 673 per month to 594 after the EOS calculator learning period. EOS calculator period. Special cause variation, displayed in red, is seen with 15 consecutive points below the previous mean. Baseline period was from July 2018 to September 2019; learning period from October 2019 to April 2020; EOS calculator period May 2020 to ongoing. The study period includes baseline period and up until September 2020. CL, centre line (mean); FBEs, full blood examinations; LCL, lower control limit; UCL, upper control limit.

### Discussion

Our study found that implementation of the EOSc reduced IVABs administered to neonates born ≥35 weeks' gestation, in the 9 months from its introduction, with a decrease seen from the start of the Learning period. Post implementation of the EOSc, IVAB use was reduced by 37%. Furthermore, there was a reduction in the rate of BC investigations, number of FBE and blood gas assessments collected. The volume of blood collected

for BC was optimised, and there were no cases of missed EOS. The reduced rate of investigation and treatment for EOS risk resulted in reduced length of stay and associated costs.

Strunk et al. report similar findings in an Australian neonatal unit.<sup>20</sup> Post implementation of the EOSc, rates of empiric IVABs in the same population decreased 12% to 7.6%, without an increase in the incidence of EOS.<sup>20</sup> Similar findings have been reported in the US by Kuzniewicz et al who found the number of BC to investigate for EOS decreased from 14.5% to 4.9%, and

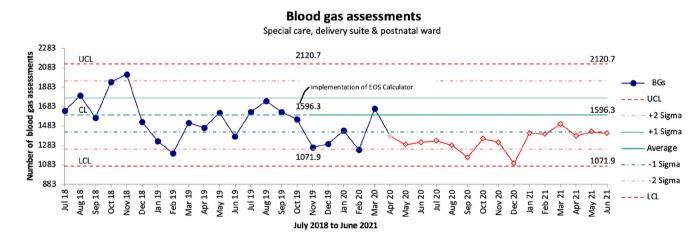


Fig. 6 X chart displaying the monthly number of capillary blood gasses for babies in the special care nursery, delivery suite and postnatal ward. The rate of capillary blood gas collection fell from an average of 1544 to 1335 per month. Special cause variation, displayed in red, is seen with 14 consecutive points below the previous mean. Baseline period was from January 2018 to September 2019; learning period from October 2019 to April 2020; EOS calculator period May 2020 to ongoing. The study period includes baseline period and up until June 2020. BGs, blood gas; CL, centre line (mean); LCL, lower control limit; UCL, upper control limit.

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the empiric IVABs rate decreased from 5.0% to 2.6% post implementation of the EOSc.<sup>2</sup> Further, meta-analysis of four studies showed an overall reduction in the IVABs use rate from 7.5% to 4.3% post implementation of the EOSc (relative risk of antibiotic use of 56% (95% CI, 53%–59%), n = 172 385).<sup>13</sup>

In our study, the magnitude of the reduction in investigation for EOS by BC draws was smaller than that observed for IVABs use. This suggests that more neonates are being investigated in our centre than the EOSc would recommend. This may reflect initial concern regarding the practice change, which was addressed with staff education reiterating that the EOSc is a decision tool and decisions regarding investigation and treatment are at clinician discretion. Despite limitations in adherence to EOSc recommendations, there was a substantial reduction in IVABs use.

Whilst the magnitude of antibiotic use reduction in our study is consistent with existing literature, the overall rate of antibiotic use in our centre remains high. Rates of antibiotic prescriptions in neonates in Australia are higher than most other high-income countries.<sup>7,20,21</sup> Contributing factors may include lack of national prescribing guidelines, and underdeveloped electronic medical record prescribing systems with associated in-built antimicrobial stewardship (AMS) functions.<sup>22</sup> Additional AMS measures are required. As well as standardised risk assessment, standardising duration of empiric antibiotics in well neonates, with duration based on BC time to positivity data, may further reduce exposure to unnecessary antibiotics.<sup>23</sup> Adapting electronic prescribing widely may standardise prescriptions and safely reduce IVAB use.<sup>22</sup>

The potential for cost savings with implementation of the EOSc is substantial.<sup>24</sup> Applying the calculated saving of \$366 per infant post implementation of the EOSc, to the 8411 babies born during the Baseline period equates to a potential saving of AUD \$3 080 781.

In addition to the avoidance of early life antibiotics, this study resulted in less use of painful IV procedures of cannula insertion and blood collection and potentially less separation of mothers and babies. There are likely broader benefits, as disruption of the mother-baby dyad can delay breastfeeding and increase the use of infant formula.<sup>25</sup>

Limitations of this study relate to the available data. Information on the timing of antibiotic administration was not available. Consequently, it was not possible to collect EOS specific antibiotic data, and any IVABs use was used as a proxy for empiric antibiotics for risk of EOS. However, data were excluded if the reason for IVABs was likely to be for a reason other than EOS (i.e., surgical prophylaxis). This will overestimate IVABs use for risk of EOS. A change in pathology databases meant that data determining baseline EOS incidence and EOS treatment rate were taken from in a different time period than the EOSc implementation period data. A limitation of our analysis is that potential confounding factors such as rates of maternal GBS colonisation or factors impacting LOS, such as number of caesarean section deliveries, gestational age and birth weight of neonates, were not adjusted for. However, we believe this is not a major source of bias as the characteristics of the hospital environment (staff and clinical protocols) and patient characteristics were unlikely to change substantially over the study period.<sup>26,27</sup> Additional limitations include that it is single centre study with a short time period of analysis, with a small sample size.

The pathology database with longest continuous data record was chosen to determine local rates. This database stopped being in use in 2014, therefore the period from 2008 to 2014 provided information for the baseline EOS incidence, gathered by a retrospective audit, of 0.67/1000. This potentially is higher than current incidence and may overestimate a neonates EOS risk.

Other potential cost savings associated with EOSc implementation, such as laboratory tests and IVABs costs were not discretely analysed. This is an important area for future study. Ongoing monitoring of EOS incidence is also a priority. Due to the low baseline incidence of EOS and short study duration, it is difficult to say conclusively that there has been no adverse effect on EOS incidence, yet the results of the current study remain reassuring.

Our study used a systematic, structured approach incorporating QI methodology to implement a significant practice change. Multidisciplinary front-line staff drove the implementation, successfully navigating barriers to implementing change. Acknowledging that contextual factors have a significant impact on QI studies, it is likely that comparable results would be seen if similar projects were undertaken in other Australasian hospitals.

### Conclusion

Our project substantially reduced the rate of IV antibiotic use in neonates born  $\geq$ 35 weeks by implementing an EOSc supported by QI methods, and in the study period, no cases of missed EOS were identified. Immediate benefits include reduced exposure to early life antibiotics and fewer painful IV procedures, and a reduction in length of stay and therefore health care costs. We acknowledge potential confounding factors were not adjusted for in our analysis and this is a limitation. More broadly, reduction in invasive assessments and treatment for risk of EOS is likely to lead to reduced separation of baby from mother with flow on effects for maternal and infant bonding and breastfeeding establishment. The use of the EOSc is now embedded in practice at our centre. We believe other neonatal units could achieve similar results with antimicrobial stewardship projects based on QI methodology.

## Acknowledgements

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# **Supporting Information**

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Data S1: Supporting Information.